Application No.: 10/559,899 Docket No.: VIP 0022USPCT EFS Amendment: March 18, 2009

In the Claims:

Please replace the claims with the following listings of claims:

1. to 5. (Canceled).

 (Currently Amended) A diagnostic system for quantitating the individual contribution of a mutation or combination of mutations to a drug resistance phenotype exhibited by an HIV strain, said system comprising

means for obtaining a genetic sequence of said HIV strain;

means for identifying the mutation pattern in said genetic sequence as compared to wild type HIV; and

means for predicting the fold resistance exhibited by said HIV strain A method for quantitating the individual contribution of a mutation or combination of mutations to a drug resistance phenotype exhibited by HIV, said-using a method comprising the steps of:

<u>la</u>) performing a linear regression analysis using data from a dataset of matching genotypes and phenotypes, wherein the log fold resistance, pFR, of each <u>said HIV</u> strain is <u>modeled modelled</u> as the sum of all the individual resistance contributions for each of said mutations or combinations of mutations that occur in HIV according to the following equation;

$$pFR = \beta_A M_A + \beta_B M_B + \beta_n M_n + \dots + \beta_Z M_Z + \varepsilon$$

wherein each <u>said</u> individual resistance contribution is calculated by multiplying a mutation factor, M_A , M_B , ..., M_Z , for each of said mutation or combination of mutations by a resistance coefficient β_A , β_B , ..., β_Z ;

wherein for a combination of mutations, <u>said</u> the mutation factor M_n represents the cooccurrence of one mutation with other one or more mutations and <u>said</u> the coefficient β_n represents the synergy or antagonism between <u>said</u> the one mutation with <u>said</u> the other one or more mutations;

wherein <u>said</u> the mutation factor assigned to each <u>said</u> mutation or combination of mutations reflects the degree to which said mutation or combination of mutations is present in said HIV strain and, if present, to which degree <u>said</u> the mutation is present in a mixture;

wherein each <u>said</u> resistance coefficient reflects the contribution of <u>said</u> the mutation or combination of mutations to <u>said</u> the fold resistance exhibited by said strain;

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wherein the error term ε , represents the difference between a <u>modeled modelled</u> prediction and an experimentally determined measurement;

2) replacing wherein the censored values in said data from said dataset of matching genotype and/phenotype database are replaced by a maximum likelihood estimation;

wherein for each iteration of said linear regression, said maximum likelihood estimation is generated according to the following steps:

wherein for each iteration of the linear regression, the following steps are performed until the predictions converge:

- a) calculating a linear regression model without said censored values;
 - b) using a phenotypic measured value V_0 of said data of said dataset of matching genotypes and phenotypes as if the censor was " = ", when a result is expressed as $-\log FR < 4$, V_0 is treated as $-\log FR = 4$;
- c) using looking at the prediction P from the said linear regression model to and apply either:

When <u>said phenotypic value is smaller than said range</u>, <u>ease</u> <u>a</u> '<'-censor <u>is applied to said value</u>:

i) $P < V_0 - 0.798 \sigma$ (center of gravity of half Gaussian distribution) Remove value from training data for the next iteration

ii)
$$V_0 - 0.798 \ \sigma \le P < V_0$$
 Use $V' = V_0 - 0.798 \ \sigma$ for the next iteration

iii) $V_0 \le P$

Use V' <u>center eentre</u> of gravity of tail (<V) of a normal distribution N (P, σ) as value for the next iteration

When <u>said phenotypic value is higher than said range</u>, <u>ease</u> <u>a</u> '>'-censor <u>is applied</u> to said value:

i) $P > V_0 + 0.798 \sigma$ (center of gravity of half Gaussian distribution)

Remove value from training data for the next iteration

ii)
$$V_0 + 0.798 \ \sigma \ge P > V_0$$
 Use $V' = V_0 - 0.798 \ \sigma$ for the next iteration

iii) $V_0 \ge P$

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Use V' <u>center eentre</u> of gravity of tail (>V) of a normal distribution N (P, σ) as value for the next iteration;

d) calculating a linear regression model and for <u>said</u> the censored values in <u>said</u> the linear regression model, either remove the datapoint from the training set, or use V' instead of the censored phenotypes measurement, as described in step c);

e) reiterating from steps b) to d) until the prediction converges;

thereby quantitating the individual contribution of said mutation or combination of mutations to <u>saida</u> drug resistance phenotype exhibited by <u>said HIV strain</u>.

7. to 16. (Canceled).